UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/990,586 | 11/21/2001 | Hing C. Wong | 71758/46943-CIP2 | 2050 |

21874 7590 09/09/2004

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

| EXAMINER | |
|---|---|
| HADDAD, MAHER M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/990,586 | WONG ET AL. | |
| | Examiner | Art Unit | |
| | Maher M. Haddad | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9,11,13-26,28,30,32,34,36,38,40,42-58,62,73 and 74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 11, 13-26, 28, 30, 32, 34, 36, 38, 40, 42-58, 62 and 73-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 8/11/04, is acknowledged.

2. Claims 1-9, 11, 13-26, 28, 30, 32, 34, 36, 38, 40, 42-58, 62 and 73-74 are pending and under examination.

3. The amendment to the specification on page 1, filed 8/11/04, deleted the text which refers to parent application 09/293,854 by strikethrough, indicates that 60/343,306 is U.S. Patent No. 6,555,319. It is suggested that a "," be inserted between the provisional application and the patent. Correction is required. Further, the specification on page 1 should be amended to indicate the relationship between 09/293,854 and 08/814,806, and the instant application.

4. Applicant's comment in the remarks recharging the IDS submitted on January 20, 2004 (citing USP 6,593,291 to Green) is no clear because no such IDS was fond in the application.

5. Claim 13 is objected to because it depends from canceled claim 12.

6. In view of the amendment filed on 8/11/04, only the following rejections are remained.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

8. Claims 1-9, 11, 13-26, 28, 30, 32, 34, 36, 38, 40 and 42-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The recitations " shown in Figure 12A (SEQ ID NOS. 73-82" and "show in Figure 13A (SEQ ID NOs. 84-96)" in claims 1 and 17, because it is unclear whether SEQ ID NO: 73-82 and 84-96 are FRs sequences or LC and HC sequences.

B. Claim 11 is indefinite in the recitation of "SEQ ID NO:98", because SEQ ID NO: 98 is a heavy chain constant sequence not a light chain constant sequence. It appears that the claim should recite SEQ ID NO: 99.

C. Claim 12 is indefinite in the recitation of "SEQ ID NO:97", because SEQ ID NO: 97 is a light chain constant sequence not a heavy chain constant sequence. It appears that the claim should recite SEQ ID NO: 98.

D. Claims 21-26 are indefinite in the recitation "at least 95% identical to" because the CDR1 for example, is only 5 amino acids and a 95% identity would lead to

4.75 amino acids (i.e., ¼ amino acid variation). Similarly 95% identical to SEQ ID NOs 9, 101, 10, 2, 6 and 7 would result in a 16.15, 16.15, 7.6, 10.45, 6.65 and 8.55 amino acid identity, respectively (i.e., 0.85, 0.85, 0.4, 0.55, 0.35 and 0.45 amino acid variation respectively). It is unclear how the skilled artisan can obtain a fraction of an amino acid variation (i.e. less that a single amino acid variation).

E. Claim 28 is indefinite because claim 28 depends from claim 17 and claim 17 recites FR1 from both HC and LC and it is unclear whether FR1 is a HC or LC. Furthermore, SEQ ID NOs: 73-82 and 84-96 do not correspond to the specific amino acid substitutions. For example in SEQ ID NO:90, there is no Q5 however, there is V5. It appears that the recited positions refer to SEQ ID NO:83.

F. Claim 30 is indefinite because claim 30 depends from claim 17 and claim 17 recites FR2 from both HC and LC and it is unclear whether FR2 is a HC or LC. Furthermore, SEQ ID NOs: 73-82 and 84-96 do not correspond to the specific amino acid substitutions. For example in SEQ ID NO:90, there is no 41H however, there is 41P. It appears that the recited positions refer to SEQ ID NO:83.

G. Claim 32 is indefinite because claim 32 depends from claim 17 and claim 17 recites FR3 from both HC and LC and it is unclear whether FR3 is a HC or LC. Furthermore, SEQ ID NOs: 73-82 and 84-96 do not correspond to the specific amino acid substitutions. For example in SEQ ID NO:90, there is no 76S however, there is 76T. It appears that the recited positions refer to SEQ ID NO:83.

H. Claim 34 is indefinite because claim 34 depends from claim 17 and claim 17 recites FR4 from both HC and LC and it is unclear whether FR4 is a HC or LC. Furthermore, SEQ ID NOs: 73-82 and 84-96 do not correspond to the specific amino acid substitutions. For example in SEQ ID NO:90, there is no 113L however, there is 113V. It appears that the recited positions refer to SEQ ID NO:83.

I. Claim 36 is indefinite in the recitation "18 to R" it is unclear what amino acid at position 18 is to be substituted. It appears that the recitation refers to 18S.

J. Claims 36, 38, 40 and 42 are indefinite, because said claims depend from claim 17 and claim 17 recites FRs 1, 2, 3, and 4 from both HC and LC and it is unclear whether FRs 1, 2, 3, 4 is a HC or LC. Furthermore, SEQ ID NOs: 73-82 and 84-96 do not correspond to the specific amino acid substitutions. It appears that the recited positions refer to SEQ ID NO:72.

K. Claim 40 is indefinite in the recitation "84A to V" it appears that the revise substitution is intended (i.e., 84V to A) because SEQ ID NO: 72 has Val at position 84 not Ala.

L. Claims 45-46 are indefinite in the recitation "at least 95% identical to" because the CDR1 for example, is only 5 amino acids and a 95% identity would lead to 4.75 amino acids (i.e., ¼ amino acid variation). Similarly 95% identical to SEQ ID NOs 9, 101, 10, 2, 6 and 7 would result in a 16.15, 16.15, 7.6, 10.45, 6.65 and 8.55 amino acid identity, respectively (i.e., 0.85, 0.85, 0.4, 0.55, 0.35 and 0.45 amino acid variation respectively). Furthermore, 95% identical to the FR2 or FR4 of SEQ ID NO: 79 would result in partial amino acid variation. It is unclear how the skilled artisan can obtain a fraction of an amino acid variation (i.e. less that a single amino acid variation).

**M.** Claim 46 stands indefinite because Claim 46((j) recites CDR3 amino acid sequence shown in Figure 12(C) (SEQ ID NO:7), however, Figure 12(C) represents CDR2. It appears that the claim should recite Figure 12(D) (SEQ ID NO:7).

**N.** Claim 45 is indefinite in the recitation "at least one murine complementarity determining region (CDR)" because the claim recites the antibody comprising on the heavy chain CDR1 (SEQ ID NO: 8), CDR2 (SEQ ID NO:9 or 101) and CDR3 (SEQ ID NO: 10). It is unclear how an antibody that comprises three murine CDRs would comprise only one or two murine CDRs.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

10. Claims 1, 6-9, 11, 13, 17-26, 28, 30, 32, 34, 36, 38, 40, 42-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized antibody that binds specifically to TF, wherein said antibody comprising the LC constant region is SEQ ID NO: 97 or 99, HC constant region is SEQ ID NO: 98 or 100, the antibody has an IgG1 (hOAT) or IgG4 (hFAT) isotype, HC CDR2 is SEQ ID NO: 90 or 101 or a specific change such as in claims 28, 30, 32 or 34, HC FR1, FR2, FR3 and FR4 of SEQ ID NO: 91, LC FR1, FR2, FR3 and FR4 of SEQ ID NO: 79 or a specific change such as in claims 36, 38, 40 or 42 (such as the antibody recited in claims 51-54) for inhibiting TF-initiated coagulation, does not reasonably provide enablement for any humanized comprises "at least one fully murine CDR" in claim 6, wherein the antibody has at least about 90% amino acid sequence identity to a human antibody in claim 8, wherein the variable region of the humanized antibody has at least about 70% amino acid sequence identity to a human antibody variable region in claim 9; a humanized antibody comprising "at least one murine complementarity determining region (CDR)", wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor X or factor IX binding to TF or TF:FVIIa and activation by TF:FvIIa thereto is inhibited in claim 17, wherein the first CDR (CDR1),

second CDR (CDR2) or third CDR (CDR3) of the heavy chain hypervariable region is at least 95% identical to the CDR1, CDR2 or CDR3 amino acid sequence of SEQ I DNO:8, 9/101 or 10, respectively, in claims 21-23, wherein the first CDR (CDR1, second CDR (CDR2), or the third CDR (CDR3) of the light chain hypervariable region is at least 95% identical to the CDR1, CDR2 or CDR3 amino acid sequence of SEQ ID NO:2, 6, 7, respectively, in claims 24-26, A humanized antibody comprising at least one murine complementarity determining region (CDR), wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor C or factor IX binding to TF or TF:FVIIa and activation by TF:FVIIa thereto is inhibited, the antibody comprising on the heavy chain: a) a first CDR (CDR1) which is "at least 95% identical to CDR1" amino acid sequence shown in Figure 13B(SEQ ID NO:8), (b0 a second CDR (CDR2) which is "at least 95% identical to CDR2" amino acid sequence shown in Figure 13C (SEQ ID NO: 9 or 101), c) a third CDR (CDR3) which is "at least 95% identical" to the CDR3 amino acid sequence shown in Figure 13D (SEQ ID NO: 10) in claim 45, the antibody further comprising on the light chain h) a first CDR (CDR1) which "at least 95% identical to CDR1 amino acid sequence shown in Figure 12B (SEQ ID NO:2), I) a second CDR(CDR2) which is at least 95% identical to CDR1 amino acid sequence shown in Figure 12C (SEQ ID NO: 6), J) a third CDR(CDR3) which is "at least 95% identical to the CDR3" amino acid sequence shown in Figure 12(C) (SEQ ID NO:6), in claim 46. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reason in the previous Office Action mailed 3/11/04.

There is insufficient guidance and direction as to make and use humanized antibodies. Claim, 6 recites "at least one full murine CDR", claim 17 recites " at least one CDR", claim 8 recites "at least about 90% amino acid sequence identity to a human antibody", claim 9 recites "the variable region of the humanized antibody has at least 70% amino acid sequence identity to a human antibody variable region" claims 21-26, 45 and 46 recite "at least 95% identical to" CDRs.

Claims 1 and 17 recite any humanized antibody wherein the CDRs are any CDRs. The specification does not provide guidance as to what CDRs are encompassed in claims 1 and 17.

Claim 20 recites 2 amino acid substitutions of being human. The examiner notes an amino acid is an amino acid irrespective of its source whether it is a human or mouse. The difference between human amino acid and murine amino acid is unclear.

Applicant's arguments, filed 8/11/04 have been fully considered, but have not been found convincing.

Applicant argues that further specificity regarding CDR number is certainly not required I view of Applicants' amendment to claim 1 and 17. Regarding Rudikoff reference, Applicant dismiss its teaching as it is "over 20 years old and no longer of any particular

importance in this filed", and "old and out-of-date reference". Further, Applicant contends that a worker would recognize that the reference as relied on is no longer that relevant, particularly as relied on and in view of substantial advances in the field since 1979. However, applicant did not dispute the facts presented by Rudikoff reference and contrary to the applicant assertions, Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Therefore, the Rudikoff reference demonstrates minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. It is unlikely that humanized antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of a tissue factor (TF) antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function.

Applicant argues that the specification does not need to teach that a humanized anibody can be made by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody. Applicant contends that such information is not generally needed for a worker to make and use the invention. Applicant submits that the specification provides several ways to make the claimed humanized antibody. Applicant contends that should a particular CDR "swapping" or other approach not work to produce the claimed antibody, the specification provides more than ample guidance about other methods that could be used to enable one to make and use the claimed invention. Applicant directed that Examiner attention to the specification on pg 35, line 9-pg 36, line 25 to show that "best fit" approach would avoid the pitfalls mentioned by the Examiner. Applicant submits that the "best fit method", wherein individual framework (FR) regions are mutagenized to resemble corresponding human FR regions. Furthermore, in the "best fit" method there is no need to swap CDRs.

Contrary to applicant assertion the claims as mended recite a humanized antibody wherein in the antibody comprises at least one fully murine complimentarity determining region (CDR) (see claim 6 for example). First it is unclear what else besides the murine CDRs applicant intended to have in the claimed humanized antibody. Second, such recitation require CDR "swapping" specially because the best fit deals with the FRs rather than CDRs. And that the language "at least one fully murine" indicates that there are more CDRs that can be either murine or non-murine such require "CDR grafting". Finally, the order of the CDRs are not specify.

Applicant submits that the claims language of claims 1 and 17 dose not require CDRs grafting. However, the claim language recites "at least one murine complementarity determining region. It appears that Applicant admits that the specification lack of guidance on how to obtain at least one murine CDR specially because the "best fit" methodology would not lead to the elimination of up to 5 CDRs from an antibody. The "best fit" method, individual framework regions are mutagenized to resemble corresponding human FR regions. There is no CDR elimination using "best fit" method

only mutations. The specification does not provide guidance on how an antibody comprising up to 6 CDRs can/cannot present in the humanized antibody.

11. Claims 1, 6-9, 11, 13, 17-26, 28, 30, 32, 34, 36, 38, 40, 42-50 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a humanized antibody that binds specifically to TF, wherein said antibody comprising the LC constant region is SEQ ID NO: 97 or 99, HC constant region is SEQ ID NO: 98 or 100, the antibody has an IgG1 (hOAT) or IgG4 (hFAT) isotype, HC CDR2 is SEQ ID NO: 90 or 101 or a specific change such as in claims 28, 30, 32 or 34, HC FR1, FR2, FR3 and FR4 of SEQ ID NO: 91, LC FR1, FR2, FR3 and FR4 of SEQ ID NO: 79 or a specific change such as in claims 36, 38, 40 or 42 (such as the antibody recited in claims 51-54) for inhibiting TF-initiated coagulation

Applicant is not in possession of any humanized comprises "at least one fully murine CDR" in claim 6, wherein the antibody has at least about 90% amino acid sequence identity to a human antibody in claim 8, wherein the variable region of the humanized antibody has at least about 70% amino acid sequence identity to a human antibody variable region in claim 9; a humanized antibody comprising "at least one murine complementarity determining region (CDR)", wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor X or factor IX binding to TF or TF:FVIIa and activation by TF:FvIIa thereto is inhibited in claim 17, wherein the first CDR (CDR1), second CDR (CDR2) or third CDR (CDR3) of the heavy chain hypervariable region is at least 95% identical to the CDR1, CDR2 or CDR3 amino acid sequence of SEQ I DNO:8, 9/101 or 10, respectively, in claims 21-23, wherein the first CDR (CDR1, second CDR (CDR2), or the third CDR (CDR3) of the light chain hypervariable region is at least 95% identical to the CDR1, CDR2 or CDR3 amino acid sequence of SEQ ID NO:2, 6, 7, respectively, in claims 24-26, A humanized antibody comprising at least one murine complementarity determining region (CDR), wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor C or factor IX binding to TF or TF:FVIIa and activation by TF:FVIIa thereto is inhibited, the antibody comprising on the heavy chain: a) a first CDR (CDR1) which is "at least 95% identical to CDR1" amino acid sequence shown in Figure 13B(SEQ ID NO:8), (b0 a second CDR (CDR2) which is "at least 95% identical to CDR2" amino acid sequence shown in Figure 13C (SEQ ID NO: 9 or 101), c) a third CDR (CDR3) which is "at least 95% identical" to the CDR3 amino acid sequence shown in Figure 13D (SEQ ID NO: 10) in claim 45, the antibody further comprising on the light chain h) a first CDR (CDR1) which "at least 95% identical to CDR1 amino acid sequence shown in Figure 12B (SEQ ID NO:2), I) a second CDR(CDR2) which is at least 95% identical to CDR1 amino acid sequence shown in Figure 12C (SEQ ID NO: 6), J) a third CDR(CDR3) which is "at least 95% identical to the CDR3" amino acid sequence shown

in Figure 12(C) (SEQ ID NO:6), in claim 46 for the same reasons set forth in the previous Office Action, mailed 3/11/04.

Applicant's arguments, filed 8/11/04, have been fully considered, but have not been found convincing.

Applicant argues that an adequate written description can be achieved by (1) complete or partial structure for the humanized antibodies that binds TF, (2) other physical and/or chemical properties, or (3) functional characteristics coupled with a known or disclosed correlation between structure and function.

However, the Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, the CDR(s) and it's anti-TF function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of variants, wherein the variant has 90% amino acid sequence identity to a human antibody or the variable region of the humanized antibody has at least about 70% amino acid sequence identity to a human antibody variable region, or 95% identical to the CDRs, 1, 2, 3 (HC and LC) which retain the features essential to the instant invention.

12. The following new ground of rejection is necessitated by the amendment submitted 8/11/04.

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed.

Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-9, 11, 13-26, 28, 30, 32, 34, 36, 38, 40, 42-58, 62 and 73-74 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-39 of U.S. Patent No. 6,555,319. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the `319 patent and the instant application are claiming the same humanized antibody, even though the `319 patent claims a humanized chimeric antibody that binds native human tissue factor to form a complex. Specially, because both patented and instant claims recite antibody that binds specifically to human tissue factor (TF) to form a complex. While claimed humanized antibody comprises at least 90%/95% amino acid sequence identity to any one of the light/heavy chain FR, the resultant antibody still read on the patented humanized antibody since at least 90% variation in FRs HC and LC of variant SEQ ID NO: 73-82 and 84-96 would read on the humanized antibody of `319 patent. It is noted that the CDRs of both instant and patented humanized antibody are derived from the same hybridoma (H36.D2.B7). Therefore, both humanized antibody binds specifically to human tissue factor (TF) to form a complex, wherein factor CX or factor IC binding to the complex and the FX or FIX activation by TF:FVIIa are inhibited.

Applicant argues that since claims 10 and 12 were not subject to the double patenting rejection then claim 1 with language from claims 10 and 12 would remove the basis for making the rejection.

However, claim 1 now recites at least about *90%* amino acid identity to any one of light/heavy chain FR sequences, the resultant antibody still read on the patented humanized antibody because variation up to 90% in the variant sequences of the FRs, wherein the CDRs of both the instant applicant and the patented are derived from the same hybridoma, would result in the patented humanized antibody.

15. No claim is allowed.

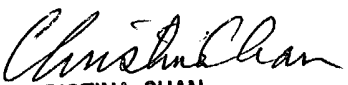
16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
September 2, 2004



CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600